

Table S1. Quality criteria for rating of POPPK models used for the simulation.

Criteria	Rating of quality assessment
Phases of clinical trials	High rating for post-marketing studies; medium rating for phase III trials and low rating for phase I-II trials
Population size	High rating if more than 100 patients included, medium rating if >100 and >50 patients, low rating if fewer than 50 patients included
Blood sample/patient	High rating if more than 4 samples per patient. Medium rating if 2 or 3 samples per patient; Low rating if fewer than 2 samples per patient
PopPK results	Are the results clearly presented? In particular, is the relationship between drug clearance and the identified covariates together with clearance inter-individual variability explicitly and correctly given? Consensual rating
Relevant covariates tested	Have the known and the relevant covariates for influencing PK of the DOACs been tested in the model? Creatinine clearance, age and weight being the minimum to get medium rate and adding of other parameters such as drug-drug interaction or hepatic enzymes are being scored as high quality
Internal validation	Goodness-of-fit plots, visual predictive check, bootstrap been correctly performed? high rating if all three criteria present, medium rating if two were present and low rating of fewer than two criteria are present
External validation	Has the model been validated on an external population? Yes or no

These criteria and classification have been previously applied to models used in the TUCUXI tool (<http://www.tucuxi.ch/>) (unpublished).

Table S2. Dabigatran: summary of studies

Study	PMID	Formulation	Aim of study	Model type	No of subjects	Validation	Origin of the data set	Type of subjects
Trocóniz IF et al (2007)	17322 149	po	Descriptive	POPPK	287	Internal	Phase II study	Thromboprophylaxis
Liesenfeld KH et al (2011)	21972 820	po	Descriptive	POPPK	9522	Internal	Phase III study	AF
Dansirikul et al (2012)	22398 858	po	Descriptive	POPPK	2045	Internal and external	Phase I study Phase II study	Healthy volunteers, AF and thromboprophylaxis
Delavenne X et al (2013)	23210 726	po	Drug-drug interaction	POPPK /PD	10	Internal	Outpatients (post marketing studies)	Healthy volunteers
Liesenfeld KH et al (2013)	23529 813	po	Descriptive	POPPK	7	Internal and external	Phase I dialysis study	End-stage renal disease patients (hemodialysis)
Ollier E et al (2015)	26392 328	po	Drug-drug interaction	POPPK /PD	9	Internal	Outpatients (post marketing studies)	Healthy volunteers

AF: atrial fibrillation

Table S3. Rivaroxaban: Summary of studies

Study	PMID	Formulation	Aim of study	Model type	No of patients	Validation	Origin of patients	Type of patients
Mueck et al (2007)	17595891	po	Descriptive	POPPK/PD	43	Internal	Phase I study	Healthy
Mueck W et al (2008)	18766262	po	Dose selection	POPPK/PD	758	Internal	Phase II studies	Thromboprophylaxis
Mueck W et al (2008)	18307374	po	Descriptive	POPPK/PD	1009	Internal	Phase II studies	Thromboprophylaxis
Mueck W et al (2011)	21895039	po	Descriptive	POPPK	870	Internal	Outpatients (post marketing studies)	VTE
Tanigawa T et al (2012)	22813718	po	Dose selection	POPPK/PD	182	Internal	Phase II studies	AF
Xu XS et al (2012)	22242932	po	Descriptive	POPPK/PD	2290	Internal	Phase III study	ACS
Kaneko M et al (2013)	23337693	po	Dose selection	POPPK/PD	597	Internal	Phase III study	AF
Girgis IG et al (2014)	24668660	po	Descriptive	POPPK/PD	161	Internal	Phase III study	AF
Barsam SJ et al (2017)	30046688	po	Effect of body weight	POPPK	101	Internal	In and outpatients (post marketing studies)	Thromboprophylaxis + VTE
Zhang et al (2017)	28679020	po	Effect of food	POPPK	285	Internal	Phase II-III studies	VTE + AF
Suzuki S et al (2017)	29773500	po	Descriptive	POPK/PD	96	Internal	Outpatients (post marketing studies)	AF
Willmann S et al (2018)	29660785	po	Descriptive	POPPK	4918	internal	Phase II-III studies	VTE + ACS + AF
Willmann S et al (2018)	30534008	po	Pediatric	POPPK	59	Internal	Phase I study	VTE
Wiesen MHJ et al (2018)	29376194	po	Residual rivaroxaban exposure after discontinuation of anticoagulant therapy in patients undergoing cardiac catheterization	POPPK	56	Internal	Inpatients (post marketing studies)	VTE + AF
Zdovc J et al (2019)	30725221	po	Pharmacogenomics	POPPK/PD	17	internal	Inpatients (post marketing studies)	Thromboprophylaxis
Speed V et al (2020)	32511863	po	Effect of bodyweight	POPPK	913	Internal	Outpatients (post marketing studies)	AF + VTE

AF: atrial fibrillation VTE: venous thrombo-embolism ACS: acute coronary syndrome

Table S4. Apixaban: Summary of studies

Study	PMID	Formulation	Aim of study	Model type	No of patients	Validation	Origin of patients	Type of patients
Leil TA et al (2014)	25229619	po	Exposure-response analysis	POPPK	5510	Internal	Phase I-II studies	Thromboprophylaxis
Byon W et al (2017)	28547774	po	Descriptive	POPPK/PD	970	Internal	Phase I-II-III studies	Healthy volunteers +VTE
Ueshima S et al (2018)	29457840	po	Pharmacogenomics	POPPK	81	Internal	In and outpatients (post marketing studies)	AF
Cirincione B et al (2018)	30259707	po	Descriptive	POPPK	4385	Internal	Phase I-II-III studies	Healthy volunteers +AF

AF: atrial fibrillation VTE: venous thrombo-embolism

Table S5. Edoxaban: Summary of studies

Study	PMID	Formulation	Aim of study	Model type	No of patients	Validation	Origin of patients	Type of patients
Salazar DE et al (2012)	22398655	po	Exposure-response analysis	POPPK	1281	Internal	Phase I-II studies	Healthy volunteers +AF
Rohatagi S et al (2012)	23014669	po	Exposure-response analysis	POPPK/PD	1753	Internal	Phase I-II studies	Healthy volunteers +AF + thromboprophylaxis
Yin O et al (2014)	25186833	po or IV	Descriptive	POPPK	278	Internal	Phase I studies	Healthy volunteers
Yin O et al (2014)	25168620	po or IV	Descriptive	POPPK	1134	Internal	Phase I-II-III studies	Healthy volunteers +AF
Song SH et al (2014)	24706516	po	Exposure-response analysis	POPPK/PD	1624	Internal	Phase I-II studies	Healthy volunteers +AF
Niebecker R et al (2015)	26218447	po	Descriptive	POPPK	3707	Internal	Phase I-III studies	Healthy volunteers +VTE
Jönsson S et al (2015)	25966665	po	Descriptive	POPPK	32	Internal	Outpatients	Patients with varying degrees of kidney function
Krekels EH et al (2016)	26951208	po	Descriptive	POPPK	10432	Internal	Phase I-III studies	Healthy volunteers +AF
Shimizu T et al (2017)	28032482	po	Descriptive	POPPK	10522	Internal and external	Phase I-III studies	Healthy volunteers +AF

VPE : venous pulmonary embolism, VTE : Venous thromboembolism, ACS : acute coronary syndrome, AF : Atrial fibrillation

Table S6. Dabigatran : demographic data

Study	Sample/patient	Age (years) (mean±SD or median (range))	Weight (kg) (mean±SD or median (range))	Ethnicity (%)	Hepatic enzymes of function (mean±SD or median (range))	Clearance Creatinine (ml/min) (Cockcroft) (mean±SD or median (range))	% Female
Trocóniz IF et al (2007)	16.04	66.97 (35-88)	78.21 (49-130)	-	-	76.16 (29.35-161.1)	53
Liesenfeld KH et al (2011)	2.91	72 (22-97)	80.3 (32.7-222.3)	Diverse	-	68.6 (16.1-361.4)	35
Dansirikul et al (2012)	4.38	46 (18-69) (healthy) 68 (21-93) (AF+OS)	69 (48-116) 80 (43-155)	Predominantly Caucasian	-	82.4 (16.0-132.4) (healthy) 87.1 (20.5-321.1) (AF + OS)	52.5 (healthy) 49.9 (AF + OS)
Delavenne X et al (2013)	11	22 (18-33)	75 (64-82)	-	-	-	-
Liesenfeld KH et al (2013)	44	38.3 (27-53)	74.0 (60-87)	-	-	-	-
Ollier E et al (2015)	11	18-35	73.0 (60-83)	-	-	-	-

AF=atrial fibrillation, OS=orthopedic surgery

Table S7. Rivaroxaban : demographic data

Study	Sample/patient	Age (mean±SD or median (range))	Weight (mean±SD or median (range))	Ethnicity	Hepatic (mean±SD or median (range))	Clearance Creatinine (ml/min) (Cockcroft) (mean±SD or median (range))	% Female
Mueck et al (2007)	42.07	32.5 (20-45)	-	Predominately caucasian	-	-	-
Mueck W et al (2008)	7.58	66 (26–93)	75 (45–120)	Predominately caucasian	-	88.1 (18.8–208)	-
Mueck W et al (2008)	7.53	65 (26–87)(hip study) and 67 (39–92) (knee study)	76 (45–125) (hip study) and 86 (50–173) (knee study)	Predominately caucasian	-	96 (33–218) (hip study) and 104 (35–259) (knee study)	-
Mueck et al (2011)	5.33	61 (18–94)	85 ± 17 (male) 73 ± 16 (female)	-	-	87.4 ± 1.5	44
Tanigawa T et al (2012)	4.63	65.6 ± 10.0	67.2 ± 10.4	Asian (Japanese)	AST (IU/L): 28.6 ±10.7; ALT (IU/L): 26.2± 13.4	79.7± 25.2	18.7
Xu XS et al (2012)	4.93	57 (24–87)	84 (36–181)	Predominately caucasian	-	96.6 (22.4–298)	22
Kaneko M et al (2013)	3.07	70.98 ± 8.31	64.45 ± 10.65	Asian (Japanese)	AST (IU/L): 27.26 ± 11.37 ; ALT (IU/L): 23.82 ± 12.85	67.41 ± 22.89	-
Girgis IG et al (2014)	4.98	65 ± 9.5	57.5 ± 9.9 (lean body weight)	Predominately caucasian	-	Creatinine = 1.09 ± 0.29 (mg/dL)	-
Barsam SJ et al (2017)	1.91	52 (20-86)	88.0 ± 23.4	Diverse	-	>80 mL/min 67%, 50-79 mL/min 25%, 30-49 mL/min 7.8%, <30 mL/min 0.2%	42
Zhang et al (2017)	5 -8	59 (31, 83) (DVT data) ; 65 (51, 81) (AF data (5th and 95th percentiles)	Lean body weight : 54.1 (40.1, 72.7) (DVT data) ; 56.6 (42.5, 73.6) (AF data) (5th and 95th percentiles)	Predominately caucasian	-	Baseline SCr (mg/dL) 0.94 (0.64, 1.28) (DVT data) ; 1.05 (0.74, 1.65) (AF data) (5th and 95th percentiles)	-
Suzuki S et al (2017)	2	68.0 ± 9.5	69.1±11.4	Asian (Japanese)	AST (IU/L) 26.0±9.7 ; ALT, (IU/L) 21.7±9.8	76.2±21.3	15.6
Willmann S et al (2018)	4.64	60.53 (11.82)	82.48 (16.87)	Predominately caucasian	-	97.74 (33.97)	39.3
Willmann S et al (2018)	3.49	6.8 ± 4.9, 6.0 (0.5–17.0)	29.5 ± 18.3, 27.7 (6.2–77.8)	Predominately caucasian	-	-	44
Wiesen MHJ et al (2018)	1.70	66.8 ± 12.9	81.7 ± 16.5	-	-	78.7 ± 29.0	41.1
Zdovc J et al (2019)	5	64 (49–82)	84 (54–125)	Predominately caucasian	-	82 (57–150) (mL/min/1.73 m ²) (Calculated according to the MDRD-4 equation)	52.94
Speed V et al (2020)	1.21	67.03 ± 15	87.75 ± 23.07	Diverse	-	86.73 ± 27.57	42.8

Table S8. Apixaban : demographic data

Study	Sample/patient	Age (Median, range)	Weight (Median, range)	Ethnicity (%)	Hepatic U/I	Clearance Creatinine (ml/min) (Cockcroft)	Female (%)
Leil TA et al (2014)	-	-	-	-	-	-	-
Byon W et al (2017) Phase I subjects	22.67	33 (18–85)	71.2 (37.7–175)	Diverse	-	112.8 (15-318)	33
Byon W et al (2017) VTE treatment subjects	3.14	61 (18–89)	84 (46.9–210)	Predominately caucasian	-	99.2 (25.3–322)	39.7
Ueshima S et al (2018)	3	68.1 (40.5-84.9)	65.0 (41.0-92.2)	Asian	ASAT 23 (13-97), ALAT 19 (5-115) Median, (range)	69.8 (30.6-145.5)	25
Cirincione B et al (2018)	2.73	68 (18–94)	81.4 (32-198.2)	Predominately caucasian	-	79.3 (11.9-319.7)	29.76

Table S9. Edoxaban : demographic data

Study	Sample/patient	Age (years) (mean±SD or median (range))	Weight (kg) (mean±SD or median (range))	Ethnicity (%)	Hepatic (mean±SD or median (range))(IU/l)	Clearance Creatinine (ml/min) (Cockcroft) (mean±SD or median (range))	% Female
Salazar DE et al (2012)	10.55	-	-	-	-	-	35.70
Rohatagi S et al (2012)	-	55 (18-88)	76 (43-128)	Predominately caucasian	AST 20 (5-120) ALT 16 (3-156)	81.1 (21.8-203.5)	47.68
Yin O et al (2014)	28.95	31.4 (18-51)	76.9 (48.8-107.0)	Diverse	-	-	12
Yin O et al (2014)	7.64	59.8 (18-105)	81.8 (31.0-165.3)	Diverse	-	88.98 (7.69- 246.80)	35.4
Song SH et al (2014)	7.05	56.2 (18-88)	77.6 (40.0-165.3)	Diverse	-	91.5 (14.1-246.8)	23.7
Niebecker R et al (2015)	4.21	32 (18-67)	79 (50-111)	Diverse	-	130 (14-247)	20
Jönsson S et al (2015)	9.5	50.1 ¹ (30.0-64.0), 56.8 ² (38.0- 65.0), 50.8 ³ (30.8- 67.0), 53.1 ⁴ (41.0- 63.0)	74.4 ¹ (58.9-89.4), 76.5 ² (60.3-91.0), 78.6 ³ (58.0-90.0), 71.7 ⁴ (56.0-95.0)	-	-	94.6 ¹ (83.0-123.0), 64.7 ² (54.0-77.0), 42.0 ³ (33.0- 49.0) and 21.8 ⁴ (14.0-27.0)	33 ¹ , 50 ² , 37.5 ³ , 62.5 ⁴
Krekels EH et al (2016)	2.59	71 (27-95) (ENGAGE AF-TIMI)	83 (32-231) (ENGAGE AF-TIMI)	Predominately caucasian	-	73 (23-434)	38
Shimizu T et al (2017)	4.35 ⁵	81 (64-91) ⁶ , 69 (36- 82) ⁷ , 73 (63-79) ⁸	54 (35-85) ⁶ , 68 (48- 85) ⁷ , 68 (50-90) ⁸	Asian (japanese) ¹	-	26.3 (17.8-29.9) ⁶ , 67.6 (50.3- 141) ⁷ , 62.5 (52.0-92.3) ⁸	21 ⁶ , 4 ⁷ , 7 ⁸

¹ Normal kidney function ² Mild renal impairment ³ moderate renal impairment ⁴ severe renal impairment ⁵ for the severe renal impairment study ⁶ patients with Severe Renal Impairment (15mg edoxaban) ⁷ patients with Normal and Mild Renal Impairment (30mg edoxaban) ⁸ patients with Normal and Mild Renal Impairment (60mg edoxaban)

Table S10. Dabigatran: Population estimates for CL/F

Study	Model description	CL/F estimate for a typical patient of the study (l/h) (RSE)	CL/F interindividual variability (%CV, RSE)	Intraindividual variability (%CV, RSE) if proportional ; (ng/ml, RSE) if additive error
Trocóniz IF et al (2007)	2 compartments, first-order absorption with a linear elimination	43.4 (0.27) (<24h) 82.1 (0.06) (>24h)	108.6 (0.16)	66.9 (0.03) (proportional, <24h) 0.375 (0.12) (Additive, <24h) 36.61 (0.05) (proportional >24h)
Liesenfeld KH et al (2011)	2 compartments, first-order absorption with a linear elimination	124 (0.70) (CL/F _{max})	-	32.8 (1.02) (proportional) 6.68 (7.81) (additive)
Dansirikul et al (2012)	2 compartments, first-order absorption with a linear elimination	107 (5.85) (healthy) 111 (2.13) (AF+OS)	-	18.4 (7.01) (proportional) 1.01 (25.5) (additive))
Delavenne X et al (2013)	2 compartments, first-order absorption with a linear elimination	14.8 (7)	-	10.5 (11) (proportional) 4.65 (16) (additive)
Liesenfeld KH et al (2013)	2 compartments, first-order absorption with a linear elimination	12.4 (28.71)	40.4 (43.01)	8.5 (24.00) (proportional)
Ollier E et al (2015)	1 compartment, first-order absorption with a linear elimination	13.7 (10)	0.156 (standard error) (32)	10.5 (7) (proportional) 2.09 (11) (additive)

Table S11. Rivaroxaban: Population estimates for CL/F

Study	Model description	CL/F estimate for a typical patient of the study (l/h) (RSE)	CL/F interindividual variability (%CV, RSE)	Intraindividual variability (%CV, RSE) if proportional ; (ng/ml, RSE) if additive error
Mueck et al (2007)	2 compartments, first-order absorption with a linear elimination	9.17 (3.1)	17.4 (19.1)	25.4 (8.2) (proportional)
Mueck W et al (2008)	1 compartment first-order absorption with a linear elimination	7.51 (4.1)	38.2 (10)	52.6 (3.0) (proportional)
Mueck W et al (2008)	1 compartment first-order absorption with a linear elimination	7.3 (4.0)	38.6 (8.3)	37.1 (4.0) (proportional)
Mueck et al (2011)	1 compartment first-order absorption with a linear elimination	5.67 (3.70)	39.9 (7.60)	40.7 (3.20) (proportional)
Tanigawa T et al (2012)	1 compartment first-order absorption with a linear elimination	4.72 (3.69)	21.3 (27.66)	40.2 (7.78) (proportional)
Xu XS et al (2012)	1 compartment first-order absorption with a linear elimination	6.48 (2.21)	31.3 (4.72)	0.35 (1.09) (additive)
Kaneko M et al (2013)	1 compartment first-order absorption with a linear elimination	4.73 (3.8)	41 (16.6)	13.1 (6.5) (proportional)
Girgis IG et al (2014)	1 compartment first-order absorption with a linear elimination	6.10 (3.9)	35.2 (14.3)	47.9 (6.2) (proportional)
Barsam SJ et al (2017)	1 compartment first-order absorption with a linear elimination	8.86 (7)	48 (99)	31 (215) (proportional); 0.016 (112) (additive error)
Zhang et al (2017)	1 compartment first-order absorption with a linear elimination	6.31 (4.01)	34.6 (11.8)	47.5 (5.22) (proportional)
Suzuki S et al (2017)	1 compartment first-order absorption with a linear elimination	4.40 (4.7%) (RSE/mean)	20.6 (28.7) (RSE/mean)	-
Willmann S et al (2018)	1 compartment first-order absorption with a linear elimination	6.58 (2.33)	26.2 (39.2)	46.6 (14.1) (proportional)
Willmann S et al (2018)	2 compartments, first-order absorption with a linear elimination	7.26 (9.38)	39.0 (2.96)	20.3 (1.54) (proportional)
Wiesen MHJ et al (2018)	2 compartments, first-order absorption with a linear elimination	4.9 (-)	27.0 (-)	-
Zdovc J et al (2019)	1 compartment first-order absorption with a linear elimination	6.12 (17.7)	80.8 (15.4)	59.5 (12.3) (proportional)
Speed V et al (2020)	1 compartment first-order absorption with a linear elimination	5.57 (5.34-5.82 95%CI)	23.02 (37.9)	46.37 (15.6)

Table S12. Apixaban : Population estimates for CL/F

Study	Model description	CL/F value (l/h) (RSE)	CL/F interindividual variability (%CV, RSE)	Intraindividual variability (%CV, RSE)
Leil TA et al (2014)	2 compartments, first-order absorption with a linear elimination	-	14.1 (37.5)	34.1 (0.328-0.356 95%CI) (proportional) 3.38 (2.02-5.64 95%CI) (additive)
Byon W et al (2017) Total subjects	2 compartments, first-order absorption with a linear elimination	4.35	33.1	Not reported
Ueshima S et al (2018)	1 compartment first-order absorption with a linear elimination	3.06	26.6 (21.5)	34 (12.0) (proportional)
Cirincione B et al (2018)	2 compartments, first-order absorption with a linear elimination	3.62		31.00 ± 0.284 (± SE) (HV and Studies Japan NVAF phase II28, Japan ACS phase II); 66.7 ± 1.87 (± SE) (Study APPRAISE 1); 45.7 ± 1.65 (± SE) (Study ARISTOTLE) (proportional)

Table S13. Edoxaban : Population estimates for CL/F

Study	Model description	CL/F estimate (l/h) (RSE)	CL/F interindividual variability (%CV, RSE)	Intraindividual variability (%CV, RSE) if proportional ; (ng/ml, RSE) if additive error
Salazar DE et al 2012	2 compartments, first-order absorption (with delayed absorption) with a linear elimination	36 (1.4)	18.1 (12.8)	-
Rohatagi S et al (2012)	2 compartments, first-order absorption (with delayed absorption) with a linear elimination	32.3 (1.2)	20.2 (12.0)	11.3 (11.0) (phase I) 66.1 (6.0) phase IIa 97.4 (5.2) phase IIb, hip study (proportional)
Yin O et al 2014	2 compartments, first-order absorption (with delayed absorption) with a linear elimination	22.6 (2.42)	9.42 (26.7)	32.1 (4.30) (proportional)
Yin O et al 2014	2 compartments, first-order absorption (with delayed absorption) with a linear elimination	11.4 (5.60)	10.1 (12.5)	30.2 (3.99) (phase I) (proportional) 79.5 (5.37) (phase II) (proportional) 50.3 (5.08) (phase III) (proportional)
Song SH et al 2014	2 compartments, first-order absorption (with delayed absorption) with a linear elimination	32.1 (1.06)	29.1 (3.68)	20.6 (0.563) for healthy volunteers study 37.3 (7.99) for PRT018 phase II study 33.9 (5.17) for the rest of studies (proportional)
Niebecker R et al 2015	2 compartments, first-order absorption (with delayed absorption) with a linear elimination	-	14.9 (7.94)	33.3 (3.95) (proportional)
Jönsson S et al 2015	2 compartments, first-order absorption (with delayed absorption) with a linear elimination	-	-	-
Krekels EH et al 2016	2 compartments, first-order absorption (with delayed absorption) with a linear elimination	-	13.6 (23.5)	28.2 (7.62) (proportional)
Shimizu T et al 2017	2 compartments, first-order absorption (with delayed absorption) with a linear elimination	-	-	-

NE : not estimated

Table S14. Dabigatran: Population estimates for pharmacokinetic parameters

Study	Vc/F estimate (l) (RSE)	V/F interindividual variability (%CV, RSE)	Vp/F estimate (l) (RSE)	Q/F (l/h) (RSE)	F	T lag (h)	ka (h-1) (RSE)	Interindividual variability Ka (%CV, RSE)
Trocóniz IF et al (2007)	30.8 (0.17)	-	136 (0.42)	13.6 (0.35)	-	-	0.022 (0.25) (<24h) 0.265 (0.11) (>24h)	29.83 (0.23) (>24h)
Liesenfeld KH et al (2011)	673 (0.98)	20.5 (13.21)	345 (fixed)	35.5 (fixed)	1.00 (fixed)	0.634 (fixed)	0.754 (fixed)	-
Dansirikul et al (2012)	756 (6.73) (healthy) 728 (3.42) (AF+OS)	25.2 (32.2)	345 (7.83)	35.5 (12.3) (healthy) 35.5(fixed) (AF+OS)	1.00 (fixed)	-	2.08 (20.0) (healthy) 0.754 (4.73) (AF+OS)	105.4 (33.7)
Delavenne X et al (2013)	48.3 (12)	0.105 (standard error) (41)	68.7 (6)	20.6 (8)	0.065 (fixed); 0.101 (1.4) in presence of clarithromycin	-	-	-
Liesenfeld KH et al (2013)	531 (22.60)	14.3 (43.07)	499 (9.42)	152 (14.34)	1.00 (fixed)	1.67 (4.56)	0.821 (16.81)	64.0 (30.24)
Ollier E et al (2015)	69.5 (6)	-	-	-	0.0565 (10) (normal absorption group) 0.0114 (6) (poor absorption group)	-	-	--

Table S15. Rivaroxaban: Population estimates for pharmacokinetic parameters

Study	Vc/F value (l) (mean, RSE)	V/F interindividual variability (%CV, RSE)	Vp/F value (l) (mean, RSE)	Q/F (l/h) (mean, RSE)	ka (h ⁻¹)	Interindividual variability Ka (%CV, RSE)
Mueck et al (2007)	<30mg 55.3 (4.3) 30mg 79.2 (9.4)	Vc/F : 30.7 (27.6) Vp/F: 38.6 (38.2)	<30mg 12.6 (11.4) 30mg 23.5 (18.6)		0.97 (15.2)	52.9 (75.4)
Mueck W et al (2008)	58.2 (4.9)	32.4 (23.0)	-		1.49 (10)	-
Mueck W et al (2008)	49.1 (4.3)	49.1 (4.3)	-		1.81 (8.3)	-
Mueck et al (2011)	54.4 (3.80)	28.8 (11.4)	-	-	1.23 (5.00)	-
Tanigawa T et al (2012)	42.9 (6.22)	24.4 (39.93%)	-		0.6 (11.43%)	68 (35.21%)
Xu XS et al (2012)	57.9 (1.16)	10.0 (3.66)	-		1.24 (3.28)	139 (0.30)
Kaneko M et al (2013)	43.8 (6.9)	63.6 (24.4%)	-		0.617 (10.7%)	58.2 (40.7%)
Girgis IG et al (2014)	79.7 (6.1)	17.6 (61.5)	-		1.16 (14.1)	-
Barsam SJ et al (2017)	101 (12)	60 (247)	-		1.21 (34)	-
Zhang et al (2017)	7.16 (3.70)	15.5 (46.2)	-		0.982 (14.0)	-
Suzuki S et al (2017)	38.2 (5.6%) (RSE/mean)	63.6 (fixed)	-		1.37 (58.9%) (RSE/mean)	44.6 (24) (RSE/mean)
Willmann S et al (2018)	62.5 (2.04)	-	-		0.821 (2.36)	39.7 (63.9)
Willmann S et al (2018)	50.9 (12)	16.7 (3.91)	13.5 (51.5)		0.717 (21.3) a for tablet and diluted suspension 0.208 (15.4) for undiluted suspension	62.8 (5.39)
Wiesen MHJ et al (2018)	39.3 (-)	-	-	0.97 (-)	1.24 (fixed)	-
Zdovc J et al (2019)	96.8 (9.70)	-	-		0.147 (14.8)	794 (14.9)
Speed V et al (2020)	59.4 (54.6-64.2 95%CI)	-	-	-	0.707 (0.552-0.862 95%CI)	-

Table S16. Apixaban: Population estimates for pharmacokinetic parameters

Study	Vc/F value (l) (RSE)	Vp/F value (l) (RSE)	V/F interindividual variability (%CV) mean (%CV, RSE)	Q/F (l/h) (RSE)	ka (h-1) (RSE)	Interindividual variability Ka (%CV, RSE)
Leil TA et al (2014)	22.9 (18.8-26.5 95%CI)	22.2 (19.8-25.3 95%CI)	6.35 (25.2)	2.60 (2.27 2.94 95%CI)	0.188 (0.161 0.215 95%CI)	28.3 (53.2)
Byon W et al (2017) Total subjects	32.1±1.16(±SE)	19.8±1.3(±SE)	23.5	1.62 (0.125)	0.44 ± 0.0209 (±SE)	50.2
Ueshima S et al (2018)	24.7 (15.8-33.6) (95%CI) ±4.54 (±SE)		56.6 (35.0)	-	0.42 (fixed)	42.0 fixed
Cirincione B et al (2018)	30±1.04 (±SE)	27.3±2.78 (±SE)	17	1.92 (0.202)	0.471±0.0218 (±SE)	51.4

Table S17. Edoxaban: Population estimates for pharmacokinetic parameters

Study	Vc/F estimate (l) (RSE)	Vp/F estimate (l) (RSE)	Vc/F interindividual variability (%CV, RSE)	Q/F (L/h) (RSE)	tlag (h)	ka (h-1) (RSE)	Interindividual variability Ka (%CV, RSE)
Salazar DE et al (2012)	244 (2.2)	90.3 (3.6)	31.0 (10.0)	6.42 (4.0)	0.421 (2.1)	5.87 (19.1)	127.7 (17.2)
Rohatagi S et al (2012)	243 (2.2)	116 (10.0)	12.2 (8.3)	5.86 (3.1)	0.425 (2.5)	7.21 (47.9)	2.787 (10.4)
Yin O et al (2014)	142 (4.31) oral 78.7 (5.64) IV	55.1 (3.94)	34.9 (9.71)	5.18 (6.93)	0.233 (NE)	1.89 (4.13)	72.8 (7.05)
Yin O et al (2014)	151 (3.03) oral 82.2 (3.65) IV	42.9 (4.59)	18.6 (8.83)	2.73 (5.64)	0.250 (NE)	1.08 (9.35)	79.4 (6.77)
Song SH et al (2014)	214 (1.87)	134 (4.53)	36.1 (4.97)	8.85 (5.29)	0.391 (0.108)	3.54 (5.96)	102 (11.3)
Niebecker R et al (2015)	209 (1.21)	92.3 (2.43)	23.2 (NE)	5.92 (2.49)	0.250 fixed (NE)	3.35 (4.15)	-
Jönsson S et al (2015)	95.4 (11.6)	54.3 (16.3)	-	5.19 (13.1)			-
Krekels EH et al (2016)	194 (1.14)	88.6 (4.04)	21.5 (not estimated)	5.75 (4.66)	0.250 fixed (NE)	2.16 (5.24)	794 (14.9)
Shimizu T et al (2017)	-	-	-	-		-	-

Table S18. Dabigatran : Significant covariates on CL/F

Study	CLcr	Serum creatinine	Age	Weight	Other
Trocóniz IF et al (2007)	↑	-	-	-	↑ with gastrin concentration
Liesenfeld KH et al (2011)	↑	-	↓	-	↓ in female patients ↓ in patients with heart failure of class II, III, or IV
Dansirikul et al (2012)	↑	-	↓	-	↓ in female patients ↓ in AF patients vs. OS patients
Delavenne X et al (2013)	-	-	-	-	-
Liesenfeld KH et al (2013)	-	-	-	-	-
Ollier E et al (2015)	-	-	-	-	-

CrCL : creatinine clearance (Cockcroft-Gault) AF=atrial fibrillation, OS=orthopedic surgery

Nb: effect if the covariates increase compared to median

Table S19. Rivaroxaban : Significant covariates on CL/F

Study	CLcr	Serum creatinine	Age	Weight	Other
Mueck et al (2007)	-	-	-	-	-
Mueck W et al (2008)	↑	-	↓	-	Study day : ↑ at steady state compared to first post-operative day ↑ with ↑ serum albumin concentration ↑ with ↑ hematocrit
Mueck W et al (2008)	↑ (knee study)	↓ (hip study)	↓ (hip study)	-	↑ with ↑ hematocrit (only after surgery) (knee study) ↓ If Female vs male (knee study)
Mueck et al (2011)	-	↓	↓	-	-
Tanigawa T et al (2012)	-	-	-	-	↓ if blood urea nitrogen ↑
Xu XS et al (2012)	-	↓	↓	-	
Kaneko M et al (2013)	↑	-	-	-	↑ with ↑ hematocrit
Girgis IG et al (2014)	-	↓	↓	-	
Suzuki S et al (2017)	↑	-	-		↓ if Mild CYP3A4/5 or Pgp inhibitors ↓ with ↑ ALT
Barsam SJ et al (2017)	↑	-	-	-	-
Zhang et al (2017)	-	↓	↓	-	no effect of food time (evening and morning)
Willmann S et al (2018)	↑	-	-	↓	↑ if CYP3A4 inducers ↓ if weak-moderate CYP3A4 inhibitors ↑ if VPE vs VTE ↓ if AF vs VTE ↑ ACS vs VTE
Willmann S et al (2018)	-	-	-	-	-
Wiesen MHJ et al (2018)	↑	-	-	-	-
Zdovc J et al (2019)	-	-	-	-	↓ if Low ABCB1 expression ↑ if high ABCB1 expression.
Speed V et al (2020)	↑	-	-	-	-

Nb: effect if the covariates increase compared to median

VPE : venous pulmonary embolism, VTE : Venous thromboembolism, ACS : acute coronary syndrome, AF : Atrial fibrillation

Table S20. Apixaban : Significant covariates on CL/F

Study	CLcr	Serum creatinine	Age	Weight	Other
Leil TA et al (2014)	-	-	-	-	For CL_{NR}/F : ↓ with ↑ in age, ↓ if female ↓ dose (>25mg/d) ↓ if surgery <4d vs ≥4d
Byon W et al (2017) Total subjects	-	-	-	-	↓ if Asian vs non-Asian ↓ if strong or moderate CYP3A4/P-gp inhibitors vs no inhibitors For CL_{NR}/F : ↓ if female
Ueshima S et al (2018)	↑	-	-	-	↑ if CYP3A5*1/*1 vs CYP3A5*1/*3 or *3/*3 genotype ↑ if ABCG2 421C/C or C/A genotype vs ABCG2 421A/A genotype
Cirincione B et al (2018)	↑	-	-	-	↓ if strong or moderate CYP3A4/P- gp inhibitors vs no inhibitors ↓ if asian vs non-Asian ↓ AF vs healthy patients ↓ if ACS vs healthy subjects ↓ if Japanese, Korean, and other Asian ethnicities vs non-Asian For CL_{NR}/F : ↓ if female

Nb: effect if the covariates increase compared to median

AF = atrial fibrillation

Table S21. Edoxaban : Significant covariates on CL/F

Study	CLcr	Serum creatinine	Age	Weight	Other
Salazar DE et al (2012)	↑	-	-	-	↓ if P-gp inhibitors (including quinidine, ketoconazole, erythromycin and amiodarone)
Rohatagi S et al (2012)	↑	-	-	-	-
Yin O et al (2014)	-	-	-	-	↓ if female
Yin O et al 2014	↑	-	-	-	For CL/F _R : ↓ if P-gp inhibitors (including quinidine, ketoconazole, erythromycin, verapamil, and amiodarone) (IV only) For CL/F _{NR} : ↑ age and ↓ with weight
Song SH et al (2014)	NP	NP	NP	NP	NP
Niebecker R et al (2015)	-	-	-	-	↓ if Pgp inhibitors (only for phase 1 studies)
Jönsson S et al (2015)	↑	-	-	-	For CL/F _R : ↑ in Asian race ↓ in AF patients
Krekels EH et al (2016)	-	-	-	-	For CL/F _{NR} : ↓ in AF patients vs healthy volunteers
Shimizu T et al (2017)	-	-	-	-	-

Nb: effect if the covariates increase compared to median

NP : not pursued

Table S22. Dabigatran: Significant covariates on Vc/F

Study	Age	Weight	Other
Trocóniz IF et al (2007)	-	-	-
Liesenfeld KH et al (2011)	-	↑	↑ with hemoglobin concentration
Dansirikul et al (2012)	-	↑	-
Delavenne X et al (2013)	-	-	-
Liesenfeld KH et al (2013)	-	-	-
Ollier E et al (2015)	-	-	-

Nb: effect if the covariates increase compared to median

Table S23. Rivaroxaban: Significant covariates on Vc /F

Study	Age	Weight	Other
Mueck et al (2007)	-	-	-
Mueck W et al (2008)	-	↑ (body surface area)	-
Mueck W et al (2008)	-	↑ (Lean body mass) (hip study) ↑ (body surface area)	-
Mueck et al (2011)	↓	↑	↓ If Female
Tanigawa T et al (2012)	-	-	-
Xu XS et al (2012)	↓	↑ (Lean body mass)	-
Kaneko M et al (2013)	-	-	-
Girgis IG et al (2014)	↓	↑ (Lean body mass)	-
Zhang et al (2017)	↓	↑ (Lean body mass)	-
Barsam SJ et al (2017)	-	-	-
Suzuki S et al (2017)	-	-	-
Willmann S et al (2018)	↓	↑	↓ If Female
Willmann S et al (2018)	-	-	-
Wiesen MHJ et al (2018)	-	-	-
Zdovc J et al (2019)	-	-	-
Speed V et al (2020)	-	↑ (Lean body mass)	-

Nb: effect if the covariates increase compared to median

Table S24. Apixaban : Significant covariates on Vc/F

Study	Age	Weight	Other
Leil TA et al (2014)	-	↑	↑ if hematocrit ↑
Byon W et al (2017) Total subjects	-	↑	-
Ueshima S et al (2018)	-	-	-
Cirincione B et al (2018)	-	↑	-

Nb: effect if the covariates increase compared to median

Table S25. Edoxaban : Significant covariates on Vc/F

Study	Age	Weight	Other
Salazar DE et al (2012)	-	↑	↓ if AF patients
Rohatagi S et al (2012)	-	-	
Yin O et al (2014)	-	-	-
Yin O et al (2014)	-	-	↓ if P-gp inhibitors (including quinidine, ketoconazole, erythromycin, verapamil, and amiodarone) (both IV and po)
Song SH et al (2014)	NP	NP	NP
Niebecker R et al (2015)	-	-	↑ in Asian race
Jönsson S et al (2015)	-	-	-
Krekels EH et al (2016)	-	-	↑ in Asian race
Shimizu T et al (2017)	-	-	-

Nb: effect if the covariates increase compared to median

NP : not pursued

Table S26. Apixaban: Significant covariates on CL_{R/F}

Study	CLcr	Serum creatinine	Age	Weight	Other
Leil TA et al (2014)	↑	-	-	-	-
Byon W et al (2017)	↑	-	-	-	-
Total subjects					
Ueshima S et al (2018)	-	-	-	-	-
Cirincione B et al (2018)	-	-	-	-	-

Nb: effect if the covariates increase compared to median

Table S27. Apixaban : Significant covariates on CL_{NR/F}

Study	CLcr	Serum creatinine	Age	Weight	Other
Leil TA et al (2014)	-		↓	-	↓ if female ↓ dose (>25mg/d) ↓ if surgery <4d vs ≥4d
Byon W et al (2017) Total subjects	-	-	↓	-	↓ if female
Ueshima S et al (2018)	-	-	-	-	-
Cirincione B et al (2018)	-	-	-	-	↓ if female

Nb: effect if the covariates increase compared to median

Table S28. Edoxaban : Significant covariates on CL_{R/F}

Study	CLcr	Serum creatinine	Age	Weight	Other
Salazar DE et al (2012)	-	-	-	-	-
Rohatagi S et al (2012)	-	-	-	-	-
Yin O et al (2014)	-	-	-	-	-
Yin O et al (2014)	-	-	-	-	↓ if P-gp inhibitors (including quinidine, ketoconazole, erythromycin, verapamil, and amiodarone) (IV only)
Song SH et al (2014)	NP	NP	NP	NP	NP
Niebecker R et al (2015)	↑	.	.	.	-
Jönsson S et al (2015)	-	-	-	-	-
Krekels EH et al (2016)	↑	-	-	-	↑ in Asian race ↓ in AF patients
Shimizu T et al (2017)	-	-	-	-	-

Nb: effect if the covariates increase compared to median

AF : atrial fibrillation

NP : not pursued

Table S29. Edoxaban : Significant covariates on CL_{NR/F}

Study	CLcr	Serum creatinine	Age	Weight	Other
Salazar DE et al (2012)	-	-	-	-	
Rohatagi S et al (2012)	-	-	-	-	-
Yin O et al (2014)	-	-	-	-	-
Yin O et al (2014)	-	-	↓	↑	-
Song SH et al (2014)	NP	NP	NP	NP	NP
Niebecker R et al (2015)	-	-	-	-	-
Jönsson S et al (2015)	-	-	-	-	-
Krekels EH et al (2016)	-	-	-	-	↓ in AF patients
Shimizu T et al (2017)	-	-	-	-	-

Nb: effect if the covariates increase compared to median

NP : not pursued

Table S30. Dabigatran: Significant covariates on F

Study	Age	Weight	Other
Trocóniz IF et al (2007)	-	-	-
Liesenfeld KH et al (2011)	-	-	↑ with verapamil, amiodarone, ↓ with coadministration of pump proton inhibitor
Dansirikul et al (2012)	-	-	-
Delavenne X et al (2013)	-	-	-
Liesenfeld KH et al (2013)	-	-	-
Ollier E et al (2015)	-	-	-

Nb: effect if the covariates increase compared to median

Table S31. Dabigatran : Significant covariates on Ka

Study	Age	Weight	Other
Trocóniz IF et al (2007)	↓	-	↓ Serum creatinine
Liesenfeld KH et al (2011)	-	-	-
Dansirikul et al (2012)			↑ with P-gp inhibitor ↓ with proton pump inhibitors
Delavenne X et al (2013)	-	-	-
Liesenfeld KH et al (2013)	-	-	-
Ollier E et al (2015)	-	-	-

Nb: effect if the covariates increase compared to median

Table S32. Apixaban: Significant covariates on Ka

Study	Administration in the evening vs administration in the morning or afternoon
Leil TA et al (2014)	-
Byon W et al (2017) Total subjects	↓
Ueshima S et al (2018)	-
Cirincione B et al (2018)	↓

Nb: effect if the covariates increase compared to median

Table S33. Edoxaban Significant covariates on Ka

Study	Age	Weight	Other
Salazar DE et al (2012)	-	-	-
Rohatagi S et al (2012)	-	-	↓ with food ↓ 6h prior to surgery vs 12h
Yin O et al (2014)	-	-	-
Yin O et al (2014)	-	-	-
Song SH et al (2014)	-	-	-
Niebecker R et al (2015)	-	-	-
Jönsson S et al (2015)	-	-	-
Krekels EH et al (2016)	-	-	-
Shimizu T et al (2017)	-	-	-

Nb: effect if the covariates increase compared to median

NP : not pursued

Table S34. Quality of the models used for simulations: Dabigatran.

Models	Phases of clinical trials	Population size	Blood sample/patients	POPPK results	Relevant covariates tested	Internal validation	External validation
Trocóniz IF et al (2007)	Red						No
Liesenfeld KH et al (2011)	Yellow		Yellow				No
Dansirikul et al (2012)	Red						Yes

Legends. High, medium, weak classification defined in table S1

Table S35. Quality of the models used for simulations: Rivaroxaban

Models	Phases of clinical trials	Population size	Blood sample size	POPPK results	Relevant covariates	Internal validation	External validation
Barsam SJ et al (2017)	High	Medium	Medium	High	Medium	Medium	No
Willmann S et al (2018)	Medium	High	Medium	High	Medium	High	Yes
Kaneko M et al (2013)	Medium	High	Medium	Medium	Medium	Medium	No
Xu XS et al (2012)	Medium	High	Medium	High	Medium	Medium	No
Suzuki S et al (2017)	High	Medium	Weak	High	Medium	Medium	No
Speed V et al (2020)	High	High	Weak	High	Medium	Medium	No

Legends. High, medium, weak classification defined in table S1

Table S36. Quality of the models used for simulations: Apixaban

Models	Phases of clinical trials	Population size	Blood sample size	POPPK results	Relevant covariates	Internal validation	External validation
Ueshima S et al (2018)	High	High	High	High	High	High	No
Leil TA et al (2014)	Medium	Medium	Not available	High	High	High	No

Legends. High, medium, weak classification defined in table S1

Table S37. Quality of the models used for simulations: Edoxaban

Models	Phases of clinical trials	Population size	Blood sample size	POPPK results	Relevant covariates	Internal validation	External validation
Krekels EH et al (2016)	High	Medium	High	Medium	Medium	Medium	No
Niebecker R et al (2015)	High	Medium	Medium	Medium	Medium	Medium	No
Yin O et al (2014)	Medium	Medium	Medium	Medium	Medium	Medium	No
Salazar DE et al (2012)	Weak	Medium	Medium	Medium	Medium	Medium	No
Rohatagi S et al (2012)	Weak	Medium	Not available	Medium	Medium	Medium	No

Legends. High, medium, weak classification defined in table S1

Table S38. Mean increases in AUC detailed for each model and different covariates: dabigatran

Study	Simulation conditions	drug dose	n=	AUC normalized to a typical patient
				mean [95% Confidence Interval]
Liesenfeld KH et al (2011)	CLCr [50-130] ml/min, Age=70	150 mg BID	1000	1.31 [1.15 – 1.47]
	CLCr [50-130] ml/min, Age=80	110mg BID	1000	1.09 [0.88 – 1.30]
	CLCr [30-49] ml/min, Age=70	110mg BID	1000	1.60 [1.39 – 1.81]
	CLCr [30-49] ml/min, Age=80	110mg BID	1000	1.67 [1.45 – 1.89]
	CLCr [15-29] ml/min, Age=70	110mg BID	1000	2.77 [2.16 – 3.37]
	CLCr [15-29] ml/min, Age=80	110mg BID	1000	2.88 [2.25 – 3.51]
	CLCr [15-29] ml/min, Age=70 (US recommendation)	75mg BID	1000	1.89 [1.47 – 2.30]
	CLCr [15-29] ml/min, Age=80 (US recommendation)	75mg BID	1000	1.97 [1.53 – 2.39]]
Trocóniz IF et al (2007)	Post-surgery thrombophylaxis patient, >24h, Gastrine=69.16 pmol/L, CLCr [50-130] ml/min	220mg OD	1000	1.21 [0.46 – 1.96]
	Post-surgery thrombophylaxis patient, >24h, Gastrine=69.16 pmol/L, CLCr [30-49] ml/min	220mg OD	1000	1.46 [0.58 – 2.34]
	Post-surgery thrombophylaxis patient, >24h, Gastrine=69.16 pmol/L, CLCr [15-29] ml/min	220mg OD	1000	2.77 [1.56 – 3.98]

	Post-surgery thrombophylaxis patient, >24h, Gastrine=34.58 pmol/L, CLCr [50-130] ml/min	220mg OD	1000	3.08 [1.79 – 4.37]
	Post-surgery thrombophylaxis patient, >24h, Gastrine=34.58 pmol/L, CLCr [30-49] ml/min	220mg OD	1000	4.41 [2.94 – 5.88]
	Post-surgery thrombophylaxis patient, >24h, Gastrine=34.58 pmol/L, CLCr [15-29] ml/min	220mg OD	1000	6.00 [4.25 – 7.76]
Dansirikul et al (2012)	AF patients, CLCr [50-130] ml/min, aged [80-100] year, P-gp inhibitor=0	110mg BID	1000	1.34 [1.016 – 1.67]
	AF patients, CLCr [50-130] ml/min, aged [80-100] year, P-gp inhibitor=1	110mg BID	1000	1.54 [1.17 – 1.92]
	AF patients, CLCr [50-130] ml/min, aged [40-79] years, P-gp inhibitor=0	150mg BID	1000	1.48 [1.10 – 1.86]
	AF patients, CLCr [50-130] ml/min, aged [40-79] years, P-gp inhibitor=1	150mg BID	1000	1.70 [1.26 – 2.14]
	AF patients, CLCr [30-49] ml/min, aged [80-100] year, P-gp inhibitor=0	110mg BID	1000	1.80 [1.51 – 2.08]
	AF patients, CLCr [30-49] ml/min, aged [80-100] year, P-gp inhibitor=1	110mg BID	1000	2.07 [1.74 – 2.39]
	AF patients, CLCr [30-49] ml/min, aged [40-79] years, P-gp inhibitor=0	110mg BID	1000	2.20 [1.93 – 2.48]
	AF patients, CLCr [30-49] ml/min, aged [40-79] years, P-gp inhibitor=1	110mg BID	1000	2.53 [2.22 – 2.85]
	AF patients, CLCr [15-29] ml/min, aged [80-100] year, P-gp inhibitor=0	110mg BID	1000	2.34 [1.98 – 2.71]
	AF patients, CLCr [15-29] ml/min, aged [80-100] year, P-gp inhibitor=1	110mg BID	1000	2.70 [2.27 – 3.12]
	AF patients, CLCr [15-29] ml/min, aged [40-79] years, P-gp inhibitor=0	110mg BID	1000	2.89 [2.53 – 3.24]

	AF patients, CLCr [15-29] ml/min, aged [40-79] years, P-gp inhibitor=1	110mg BID	1000	3.32 [2.91 – 3.73]
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CLCr: creatinine clearance calculated using the Cockcroft –Gault equation, NVAF: nonvalvular atrial fibrillation, AF: atrial fibrillation, VTE: venous thromboembolism, P-gp: P-glycoprotein

Table S39. Mean increases in AUC detailed for each model and different covariates: rivaroxaban

Study	Simulation conditions	n=	drug dose	AUC normalized to a typical patient
				mean [95% Confidence Interval]
Barsam SJ et al (2017)	VTE patient, CLCr [50-130] ml/min	1000	20mg OD	1.12 [0.22 – 2.022]
	VTE patient, CLCr [30-49] ml/min	1000	20mg OD	1.63 [0.66 – 2.60]
	VTE patient, CLCr [15-29] ml/min	1000	15mg OD	1.56 [0.33 – 2.79]
Willmann S et al (2018)	AF patient,, CLCr [50-130] ml/min, Without co-medication	1000	20mg OD	1.17 [0.59 – 1.75]
	AF patient,, CLCr [50-130] ml/min, Moderate CYP3A4 inhibitor=1	1000	20mg OD	1.23 [0.63 – 1.83]
	AF patient,, CLCr [50-130] ml/min, Strong CYP3A4 inhibitor=1	1000	20mg OD	1.26 [0.64 – 1.87]
	AF patient,, CLCr [50-130] ml/min, Strong CYP3A4 inhibitor=1, P-gp inhibitor=1	1000	20mg OD	1.33 [0.71 – 1.93]
	AF patient,, CLCr [30-49] ml/min, Without co-medication	1000	15mg OD	1.25 [0.66 – 1.86]
	AF patient,, CLCr [30-49] ml/min, Without co-medication	1000	20mg OD	1.42 [0.73 – 2.11]
	AF patient,, CLCr [30-49] ml/min, P-gp inhibitor=1	1000	15mg OD	1.26 [0.86 – 2.42]
	AF patient,, CLCr [30-49] ml/min, P-gp inhibitor=1	1000	20mg OD	1.64 [0.65 – 1.86]

	AF patient., CLCr [30-49] ml/min, Moderate CYP3A4 inhibitor=1	1000	15mg OD	1.44 [0.77 – 2.12]
	AF patient., CLCr [30-49] ml/min, Moderate CYP3A4 inhibitor=1	1000	20mg OD	1.73 [0.93 – 2.53]
	AF patient., CLCr [30-49] ml/min, Strong CYP3A4 inhibitor=1	1000	15mg OD	1.27 [0.65 – 1.88]
	AF patient., CLCr [30-49] ml/min, Strong CYP3A4 inhibitor=1	1000	20mg OD	1.92 [1.03 – 2.80]
	AF patient., CLCr [30-49] ml/min Strong CYP3A4 inhibitor=1, P-gp inhibitor=1	1000	15 mg OD	1.32 [0.65 – 1.98]
	AF patient., CLCr [30-49] ml/min Strong CYP3A4 inhibitor=1, P-gp inhibitor=1	1000	20mg OD	2.01 [1.03 – 2.99]
	AF patient., CLCr [15-29] ml/min, Without co-medication	1000	15 mg OD	1.58 [0.81 – 2.35]
	AF patient., CLCr [15-29] ml/min, P-gp inhibitor=1	1000	15 mg OD	1.61 [0.87 – 2.38]
	AF patient., CLCr [15-29] ml/min, Moderate CYP3A4 inhibitor=1	1000	15 mg OD	1.85 [1.01 – 2.69]
	AF patient., CLCr [15-29] ml/min, Strong CYP3A4 inhibitor=1	1000	15 mg OD	1.89 [1.23 – 2.54]
	AF patient., CLCr [15-29] ml/min, Strong CYP3A4 inhibitor=1, P-gp inhibitor=1	1000	15 mg OD	1.97 [1.21 – 2.73]
	CLCr [50-130] ml/min	1000	20mg OD	0.90 [0.46 – 1.36]
Kaneko M et al (2013)	CLCr [30-49] ml/min	1000	20mg OD	1.45 [0.70 – 2.14]
	CLCr [30-49] ml/min	1000	15mg OD	1.07 [0.53 – 1.61]
	CLCr [15-29] ml/min	1000	15mg OD	1.61 [0.81 – 2.43]

Xu XS et al (2012)	Without DVT patient,, SC=1,3 mg/dL	1000	20mg OD	1.06 [0.65 – 1.47]
	Without DVT patient, BW=80 kg, SC=1,9 mg/dL	1000	20mg OD	1.17 [0.70 – 1.59]
	Without DVT patient, BW=90 kg, SC=3,2 mg/dL	1000	15 mg OD	1.14 [0.69 – 1.84]
Suzuki S et al (2017)	AF patient, CLCr [50-130] ml/min, ALT=25 U/L(normal level), P-gp inhibitor=0	1000	20mg OD	1.01 [0.69 – 1.71]
	AF patient, CLCr [50-130] ml/min, ALT=25 U/L (normal level), P-gp inhibitor=1	1000	20mg OD	1.51 [1.06 – 1.87]
	AF patient, CLCr [50-130] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=0	1000	20mg OD	1.49 [1.05 – 2.54]
	AF patient, CLCr [50-130] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=1	1000	20mg OD	2.16 [1.50 – 3.65]
	AF patient, CLCr [50-130] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=0	1000	20mg OD	1.90 [1.01 – 2.91]
	AF patient, CLCr [50-130] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=1	1000	20mg OD	2.67 [1.23 – 3.90]
	AF patient, CLCr [30-49] ml/min, ALT=25 U/L(normal level), P-gp inhibitor=0	1000	20mg OD	1.33 [0.95 – 2.28]
	AF patient, CLCr [30-49] ml/min, ALT=25 U/L(normal level), P-gp inhibitor=0	1000	15mg OD	1.00 [0.7 – 1.70]
	AF patient, CLCr [30-49] ml/min, ALT=25 U/L (normal level), P-gp inhibitor=1	1000	20mg OD	1.95 [1.39 – 3.34]
	AF patient, CLCr [30-49] ml/min, ALT=25 U/L (normal level), P-gp inhibitor=1	1000	15mg OD	1.45 [1.04 – 2.49]
	AF patient, CLCr [30-49] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=0	1000	20mg OD	1.90 [1.32 – 3.22]
	AF patient, CLCr [30-49] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=0	1000	15mg OD	1.43 [1.02 – 2.45]

	AF patient, CLCr [30-49] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=1	1000	20mg OD	2.78 [1.94 – 4.72]
	AF patient, CLCr [30-49] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=1	1000	15mg OD	2.10 [1.50 – 3.60]
	AF patient, CLCr [30-49] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=0	1000	20mg OD	2.24 [1.55 – 3.79]
	AF patient, CLCr [30-49] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=0	1000	15mg OD	1.68 [1.18 – 2.85]
	AF patient, CLCr [30-49] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=1	1000	20mg OD	3.24 [2.32 – 5.56]
	AF patient, CLCr [30-49] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=1	1000	15mg OD	2.45 [1.74 – 4.20]
	AF patient, CLCr [15-29] ml/min, ALT=25 U/L (normal level), P-gp inhibitor=0	1000	15mg OD	1.64 [1.16 – 2.80]
	AF patient, CLCr [15-29] ml/min, ALT=25 U/L (normal level), P-gp inhibitor=1	1000	15mg OD	2.38 [1.70 – 4.08]
	AF patient, CLCr [15-29] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=0	1000	15mg OD	2.34 [1.62 – 3.95]
	AF patient, CLCr [15-29] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=1	1000	15mg OD	3.35 [2.43 – 5.78]
	AF patient, CLCr [15-29] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=0	1000	15mg OD	2.73 [1.94 – 4.67]
	AF patient, CLCr [15-29] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=1	1000	15mg OD	4.02 [2.82 – 6.85]
Speed V et al (2020)	AF/VTE patients, CLCrLBW [50-130] ml/min	1000	20mg OD	1.06 [0.69 – 1.43]
	AF/VTE patients, CLCrLBW [50-130] ml/min	1000	15mg OD	1.15 [0.69 – 1.43]
	AF/VTE patients, CLCrLBW [30-49] ml/min	1000	20mg OD	1.53 [1.12 – 1.96]

	AF/VTE patients, CLCrLBW [30-49] ml/min	1000	15mg OD	1.47 [1.05 – 1.90]
	AF/VTE patients, CLCrLBW [15-29] ml/min	1000	20mg OD	1.96 [1.43 – 2.49]

CLCr: creatinine clearance calculated using the Cockcroft –Gault equation, BW: body weight, SC : serum creatinine, VTE: Venous Thromboembolism, DVT: Deep vein thrombosis, AF: Atrial fibrillation, CLCrLBW: creatinine clearance calculated using the Cockcroft –Gault equation applying lean body weight to calculation

Table S40. Mean increases in AUC detailed for each model and different covariates: apixaban

Study	Simulation conditions	n=	drug dose	AUC normalized to a typical patient
				mean [95% Confidence Interval]
Ueshima S et al 2018	CLCr [50-130] ml/min, CYP3A5=0, ABCG2 421A/A = 0	1000	5mg BID	1.18 [0.74 – 1.63]
	CLCr [50-130] ml/min, CYP3A5=1, ABCG2 421A/A = 0	1000	5mg BID	1.36 [0.80 – 1.91]
	CLCr [50-130] ml/min, CYP3A5=0, ABCG2 421A/A = 1	1000	5mg BID	1.30 [0.80 – 1.81]
	CLCr [50-130] ml/min, CYP3A5=1, ABCG2 421A/A = 1	1000	5mg BID	1.57 [0.91 – 2.07]
	CLCr [30-49] ml/min, CYP3A5=0, ABCG2 421A/A = 0	1000	5mg BID	1.36 [0.85 – 1.87]
	CLCr [30-49] ml/min, CYP3A5=1, ABCG2 421A/A = 0	1000	5mg BID	1.99 [1.24 – 2.75]
	CLCr [30-49] ml/min, CYP3A5=0, ABCG2 421A/A = 1	1000	5mg BID	1.94 [1.17 – 2.71]
	CLCr [30-49] ml/min, CYP3A5=1, ABCG2 421A/A = 1	1000	5mg BID	2.56 [1.52 – 3.61]
	CLCr [30-49] ml/min, CYP3A5=0, ABCG2 421A/A = 0	1000	2.5mg BID	0.68 [0.42 – 1.12]
	CLCr [30-49] ml/min, CYP3A5=1, ABCG2 421A/A = 0	1000	2.5mg BID	1.00 [0.62 – 1.44]

	CLCr [30-49] ml/min, CYP3A5=0, ABCG2 421A/A = 1	1000	2.5mg BID	0.97 [0.58 – 1.36]
	CLCr [30-49] ml/min, CYP3A5=1, ABCG2 421A/A = 1	1000	2.5mg BID	1.28 [0.76 – 1.80]
	CLCr [15-29] ml/min, CYP3A5=0, ABCG2 421A/A = 0	1000	2.5mg BID	0.91 [0.55 – 1.35]
	CLCr [15-29] ml/min, CYP3A5=1, ABCG2 421A/A = 0	1000	2.5mg BID	1.33 [0.81 – 1.77]
	CLCr [15-29] ml/min, CYP3A5=0, ABCG2 421A/A = 1	1000	2.5mg BID	1.25 [0.77 – 1.72]
	CLCr [15-29] ml/min, CYP3A5=1, ABCG2 421A/A = 1	1000	2.5mg BID	1.79 [1.10 – 2.48]
Leil TA et al (2014)	Orthopedic surgery patient (>4 days), Age=60, CLCr [50-130] ml/min	1000	2.5mg BID	1.10 [0.44 – 1.77]
	Orthopedic surgery patient (>4 days), Age=70, CLCr [50-130] ml/min	1000	2.5mg BID	1.12 [0.45 – 1.69]
	Orthopedic surgery patient (>4 days), Age=80, CLCr [50-130] ml/min	1000	2.5mg BID	1.14 [0.46 – 1.70]
	Orthopedic surgery patient (>4 days), Age=90, CLCr [50-130] ml/min	1000	2.5mg BID	1.16 [0.49 – 1.72]
	Orthopedic surgery patient (>4 days), Age=60, CLCr [30-49] ml/min	1000	2.5mg BID	1.58 [0.71 – 2.25]
	Orthopedic surgery patient (>4 days), Age=70, CLCr [30-49] ml/min	1000	2.5mg BID	1.59 [0.73 – 2.28]
	Orthopedic surgery patient (>4 days), Age=80, CLCr [30-49] ml/min	1000	2.5mg BID	1.63 [0.69 – 2.37]
	Orthopedic surgery patient (>4 days), Age=90, CLCr [30-49] ml/min	1000	2.5mg BID	1.69 [0.75 – 2.43]
	Orthopedic surgery patient (>4 days), Age=60, CLCr [15-29] ml/min	1000	2.5mg BID	1.67 [0.75 – 2.38]

	Orthopedic surgery patient (>4 days), Age=70, CLCr [15-29] ml/min	1000	2.5mg BID	1.70 [0.77 – 2.40]
	Orthopedic surgery patient (>4 days), Age=80, CLCr [15-29] ml/min	1000	2.5mg BID	1.76 [0.80 – 2.51]
	Orthopedic surgery patient (>4 days), Age=90, CLCr [15-29] ml/min	1000	2.5mg BID	1.81 [0.77 – 2.61]

If patients had the CYP3A51/3 or 3/3 genotype, then the dichotomous parameter CYP3A5=1, otherwise it was set to 0. If patients had the ABCG2 421A/A genotype, then the dichotomous parameter ABCG2=1, otherwise it was set to 0. CLCr: creatinine clearance calculated using the Cockcroft –Gault equation.

Table S41. Mean increases in AUC detailed for each model and different covariates: edoxaban

Study	Simulation conditions	n=	drug dose	AUC normalized to a typical patient
				mean [95% Confidence Interval]
KrekeH et al 2016	NVAF patient. CLCr [50-130] ml/min. P-gp Inhibitor=0	1000	60mg OD	1.20 [0.88 – 1.53]
	NVAF patient. CLCr [50-130] ml/min. P-gp Inhibitor=1	1000	30mg OD	0.68 [0.51 – 0.85]
	NVAF patient. CLCr [30-49] ml/min. P-gp Inhibitor=0	1000	60mg OD	1.75 [0.70 – 2.80]
	NVAF patient. CLCr [30-49] ml/min. P-gp Inhibitor=1	1000	60mg OD	1.91 [0.92 – 2.90]
	NVAF patient. CLCr [30-49] ml/min. P-gp Inhibitor=0	1000	30mg OD	0.88 [0.70 – 1.10]
	NVAF patient. CLCr [30-49] ml/min. P-gp Inhibitor=1	1000	30mg OD	0.95 [0.85 – 1.05]
	NVAF patient. CLCr [15-29] ml/min. P-gp Inhibitor=0	1000	30mg OD	1.13 [0.88 – 1.37]
	NVAF patient. CLCr [15-29] ml/min. P-gp Inhibitor=1	1000	30mg OD	1.33 [0.98 – 1.68]

Niebecker R et al 2015	CLCr [50-130] ml/min. BW [60-120] kg. P-gp Inhibitor=0	1000	60mg OD	1.03 [0.74 – 1.32]
	CLCr [50-130] ml/min. BW [40-59] kg. P-gp Inhibitor=0	1000	60mg OD	1.24 [0.33 – 2.16]
	CLCr [50-130] ml/min. BW [60-120] kg. P-gp Inhibitor=1	1000	30mg OD	0.68 [0.40 – 0.94]
	CLCr [50-130] ml/min. BW [40-59] kg. P-gp Inhibitor=1	1000	30mg OD	0.73 [0.45 – 1.01]
	CLCr [50-130] ml/min. BW [60-120] kg. P-gp Inhibitor=1	1000	30mg OD	0.80 [0.49 – 1.10]
	CLCr [30-49]ml/min. BW [60-120] kg. P-gp Inhibitor=0	1000	60mg OD	1.49 [0.52 – 2.47]
	CLCr [30-49]ml/min. BW [60-120] kg. P-gp Inhibitor=1	1000	60mg OD	1.68 [0.58 – 2.78]
	CLCr [30-49]ml/min. BW [40-59] kg. P-gp Inhibitor=0	1000	60mg OD	1.86 [0.72 - 3.00]
	CLCr [30-49]ml/min. BW [[40-59] kg. P-gp Inhibitor=1	1000	60mg OD	2.04 [0.80 – 3.27]
	CLCr [30-49]ml/min. BW [60-120] kg. P-gp Inhibitor=0	1000	30mg OD	0.80 [0.52 – 1.09]
	CLCr [30-49]ml/min. BW [60-120] kg. P-gp Inhibitor=1	1000	30mg OD	0.89 [0.58 – 1.19]
	CLCr [30-49]ml/min. BW [40-59] kg. P-gp Inhibitor=0	1000	30mg OD	0.94 [0.72 – 1.15]
	CLCr [30-49]ml/min. BW [40-59] kg. P-gp Inhibitor=1	1000	30mg OD	1.04 [0.80 – 1.28]
	CLCr[15-29] ml/min. BW [60-120] kg. P-gp Inhibitor=0	1000	30mg OD	0.91 [0.60 – 1.21]
	CLCr[15-29] ml/min. BW [60-120] kg. P-gp Inhibitor=1	1000	30mg OD	1.00 [0.67 – 1.32]

Yin O et al 2014	CLCr [15-29]ml/min. BW [40-59] kg. P-gp Inhibitor=0	1000	30mg OD	1.14 [0.86 – 1.41]
	CLCr [15-29]ml/min. BW [40-59] kg. P-gp Inhibitor=1	1000	30mg OD	1.27 [0.96 – 1.58]
	CLCr [50-130] ml/min. BW [60-120] kg. Amiodarone=0	1000	60mg OD	1.06 [0.82 – 1.30]
	CLCr [50-130] ml/min. BW [40-59] kg. Amiodarone=0	1000	60mg OD	1.25 [0.95 – 1.54]
	CLCr [50-130] ml/min. BW [40-59] kg. Amiodarone=0	1000	30mg OD	0.82 [0.49 – 1.06]
	CLCr [50-130] ml/min. BW [60-120] kg. Amiodarone=1	1000	60mg OD	1.36 [1.06 – 1.66]
	CLCr [50-130] ml/min. BW [40-59] kg. Amiodarone=1	1000	30mg OD	0.92 [0.64 – 1.20]
	CLCr [30-49] ml/min. BW [60-120] kg. Amiodarone=0	1000	60mg OD	1.51 [0.53 – 2.49]
	CLCr [30-49] ml/min. BW [60-120] kg. Amiodarone=1	1000	60mg OD	1.77 [0.69 – 2.85]
	CLCr [30-49] ml/min. BW [40-59] kg. Amiodarone=0	1000	60mg OD	2.01 [0.46 – 2.38]
	CLCr [30-49] ml/min. BW [40-59] kg. Amiodarone=1	1000	60mg OD	2.19 [0.91 – 3.47]
	CLCr [30-49] ml/min. BW [60-120] kg. Amiodarone=0	1000	30mg OD	0.76 [0.54 – 0.98]

Salazar DE et al 2012	CLCr [15-29] ml/min. BW [60-120] kg. Amiodarone=0	1000	30mg OD	0.73 [0.59 – 0.88]
	CLCr [15-29] ml/min. BW [60-120] kg. Amiodarone=1	1000	30mg OD	0.96 [0.79 – 1.13]
	CLCr [15-29] ml/min. BW [40-59] kg. Amiodarone=0	1000	30mg OD	0.95 [0.76 – 1.14]
	CLCr [15-29] ml/min. BW [40-59] kg. Amiodarone=1	1000	30mg OD	1.25 [1.02 – 1.47]
	NVAF patient. CLCr [50-130] ml/min. P-gp Inhibitor=0	1000	60mg OD	0.97 [0.71 – 1.24]
	NVAF patient. CLCr [50-130] ml/min. P-gp Inhibitor=1 (Amiodarone)	1000	30mg OD	0.79 [0.60 – 0.98]
	NVAF patient. CLCr [50-130] ml/min. P-gp Inhibitor=1 (Ketoconazole)	1000	30mg OD	0.95 [0.71 – 1.19]
	NVAF patient. CLCr [30-49] ml/min. P-gp Inhibitor=0	1000	60mg OD	1.40 [1.14 – 1.66]
	NVAF patient. CLCr [30-49] ml/min. P-gp Inhibitor=1 (Amiodarone)	1000	60mg OD	2.01 [1.68 – 2.34]
	NVAF patient. CLCr [30-49] ml/min. P-gp Inhibitor=1 (Ketoconazole)	1000	60mg OD	2.22 [1.83 – 2.62]

	NVAF patient. CLCr [15-29] ml/min. P-gp Inhibitor=1 (Ketoconazole)	1000	30mg OD	1.40 [1.05 – 1.75]
Rohatagi S et al (2012)	CLCr [50-130] ml/min	1000	60mg OD	1.11 [0.77 – 1.46]
	CLCr [30-49] ml/min	1000	60mg OD	1.47 [1.05 – 1.76]
	CLCr [30-49] ml/min	1000	30mg OD	0.73 [0.53 – 0.95]
	CLCr [15-29] ml/min	1000	30mg OD	0.90 [0.65 – 1.15]

CLCr: creatinine clearance calculated using the Cockcroft –Gault equation. NVAF: nonvalvular atrial fibrillation. AF: atrial fibrillation. VTE: venous thromboembolism. Pgp: P-glycoprotein

Data S1: Equations for CL/F simulations for dabigatran

Trocóniz IF et al (2007) PMID 17322149 ¹

$$CL/F_{<24h} = \left[\theta_{CL(<24h)} \cdot \left(1 + \theta_{GAST1} \cdot \frac{GAST}{34.58} \right) \right]$$

$$CL/F_{>24h} = \left[\theta_{CL(>24h)} \cdot \frac{CrCL}{76.17} \cdot \left(1 + \theta_{GAST2} \cdot \frac{GAST}{34.58} \right) \right]$$

$$\theta_{CL(<24h)} = 43.4 \text{ mL/min}; \theta_{GAST1} = 0.633 \text{ pmol/L}; \theta_{CL(>24h)} = 82.1 \text{ mL/min}; \theta_{GAST2} = 0.294 \text{ pmol/L}$$

Liesenfeld KH et al (2011) PMID 21972820 ²

$$CL/F = \theta_{CLmax} \cdot CrCL^{**} \theta_{POWERCrCL} / (\theta_{EC50CrCL}^{**} \theta_{POWERCrCL} + CrCL^{**} \theta_{POWERCLcr}) \cdot (1 + \theta_{Age} * [Age - 72]) \cdot \theta_{Ethn} \cdot \theta_{HF} \cdot \theta_{Sex}$$

$$\theta_{CLmax} = 124 \text{ L/h}; \theta_{POWERCrCL} = 1.29; \theta_{EC50CrCL} = 56.7 \text{ mL/min}; \theta_{Age} = -0.41\%/\text{year}; \theta_{Ethn} = 0.797; \theta_{HF} = 0.933; \theta_{Sex} = 0.917$$

Dansirikul et al (2012) PMID 22398858 ³

$$CL/F = \theta_{CL} \cdot (1 + \theta_{Age} \cdot [Age - 68]) \cdot \theta_{AF} \cdot \theta_{Female}$$

$$If CL/F < 120 \text{ mL/min}: CL/F = \theta_{CL} \cdot (1 + \theta_{CrCL} \cdot [CLCr - 120]) \cdot (1 + \theta_{AGE} \cdot [AGE - 68]) \cdot \theta_{AF} \cdot \theta_{FEMALE}$$

$$F = \theta_F \cdot \theta_{Pgp} \cdot \theta_{PPI}$$

$$\theta_{CL} = 111 \text{ (l/h)}; \theta_{AGE} = -0.00662; \theta_{AF} = 0.939; \theta_{FEMALE} = 0.875; \theta_F = 1; \theta_{Pgp} = 1.150; \theta_{PPI} = 0.854$$

(15-29, 30-49, 50-130] ml/min), Age <80 ou > 80, Pgp inhibitor or not, 110mg od or bid, 150mg od or bid

Data S2: Equations for CL/F simulations for rivaroxaban

Barsam SJ et al (2017) PMID 30046688 ⁴

$$CL = CL_{POP} \cdot \left(\frac{CrCL}{79} \right)^{0.434}$$

$$CL_{POP} = 8.86 \text{ (L/h)}$$

Willmann S et al (2018) PMID 29660785 ⁵

$$CL/F = CL_{TV}/F \cdot \left(\frac{CrCL}{93} \right)^{\theta_{CL/F,CrCL}} \cdot \left(\frac{WT}{81} \right)^{\theta_{CL/F,WT}} \cdot COMED \cdot STUDY$$

$$COMED = \begin{cases} 1 & \text{if no co-medication} \\ \theta_{CL/F,Pgp} = 0.966 & \text{co-medication with PGP inhibitor} \\ \theta_{CL/F,Strong\ 3A4\ inh} = 0.978 & \text{co-medication with strong CYP 3A4 inhibitor} \\ \theta_{CL/F,Medium\ 3A4\ inh} = 0.863 & \text{co-medication with medium CYP 3A4 inhibitor} \\ \theta_{CL/F,Weak\ 3A4\ inh} = 0.939 & \text{co-medication with weak CYP 3A4 inhibitor} \\ \theta_{CL/F,3A4\ ind} = 1.30 & \text{co-medication with CYP 3A4 inducer} \end{cases}$$

$$STUDY = \begin{cases} 1 & \text{if DVT (Studies 11223 and 11528)} \\ \theta_{CL/F,AF} = 0.849 & \text{AF (Study 3001)} \\ \theta_{CL/F,ACS} = 1.14 & \text{ACS (Study 2001)} \\ \theta_{CL/F,VTE\ \leq 72h} = 1.04 & \text{VTE (Studies 10933, 10945 and 11527), \leq 72 h} \\ \theta_{CL/F,VTE\ > 72h} = 1.29 & \text{VTE, > 72 hr after first dose} \end{cases}$$

Kaneko M et al (2013) PMID 23337693 ⁶

$$CL/F = CL_{pop} \cdot \left(\frac{CrCl}{67.11} \right)^{0.159}$$

$$CL/F = CL_{pop} \cdot (1 - 0.0132 \cdot [HCT - 42.14])$$

$$CL_{pop}/F = 4.73 \text{ (L/h)}$$

CrCL, creatinine clearance; HCT, hematocrit

Xu XS et al (2012) PMID 22242932 ⁷

$$CL/F = CL/F_{pop} \cdot (1 - 0.00112 \cdot [Age - 57] - 0.151 \cdot [SCr - 0.95])$$

$$CL/F_{pop} = 6.48 \text{ (L/h)}$$

SCR, serum creatinine; LBM, lean body mass

Suzuki S et al (2017) PMID 29773500 ⁸

$$CL/F = 4.40 \cdot \left(\frac{CrCL}{75} \right)^{0.324} \cdot \left(\frac{ALT}{22} \right)^{-0.225} \cdot (1 - 0.319(IF\ INH))$$

CrCL, creatinine clearance; ALT, alanine aminotransferase; INH: CYP3A4/5 or Pgp moderate inhibitors

Speed V et al (2020) PMID 32511863 ⁹

$$CL/F = CL/F_{pop} \cdot \left(\frac{CrCLLBW}{55} \right)^{0.446}$$

$$CL/F_{pop} = 5.57 \text{ (L/h)}$$

CrCL, creatinine clearance calculated using CG applying lean body weight to calculation

Data S3: Equations for CL/F simulations for apixaban

Ueshima S et al 2018 PMID 29457840 ¹⁰

$$CL/F = 1.53 \times \left\{ \left(\frac{CLCr}{70} \right)^{0.7} + 0.312^{CYP3A5} \times 0.341^{ABCG2} \right\}$$

If patients had the CYP3A5*1/*3 or *3/*3 genotype, then the dichotomous parameter CYP3A5 was equal to 1, otherwise it was set to 0. If patients had the ABCG2 421A/A genotype, then the dichotomous parameter ABCG2 was equal to 1, otherwise it was set to 0. CLCr: creatinine clearance calculated using the Cockcroft –Gault equation.

Leil TA et al (2014) PMID 25229619 ¹¹

$$CL/F = \left[\frac{CL_{R,MAX}/F \times cCrCL^{G1}}{cCrCL_{50}^{G1} + cCrCL^{G1}} + CL_{NR,REF}/F \cdot \left(\frac{Age}{Age_{REF}} \right)^{CL_{NR,Age}} \cdot e^{(CL_{Sex} \cdot Sex)} \cdot e^{(CL_{TDD} \cdot Sw2)} \right] \cdot e^{(CL_{D<4} \cdot Sw)} \cdot e^{(CL_{D \geq 4} \cdot Sw)}$$

$CL_{R,MAX}/F = 2.09$; $cCrCL50$ (ml/min) = 74; $CL_{NR,REF}/F = 2.66$; Age_{REF} (Y) = 67; $CL_{Sex} = -0.179$ (if female); $CL_{TDD} = 0.362$; $CL_{D<4} = 0.274$ (surgery < 4d); $CL_{D \geq 4} = -0.120$ (surgery \geq 4d)
where $CL_{NR,REF}/F$ is typical value of CL_{NR} for a male non-surgical subject receiving a total daily dose of apixaban that is not greater than 25 mg. $CL_{R,MAX}/F$ is the maximum $CL_{R,F}$, $cCrCL50$ is the $cCrCL$ value at 50% for an $CL_{R,F}$ that is half of $CL_{R,MAX}/F$ and $G1$ is the shape parameter controlling the steepness of the $CL_{R,F} \sim cCrCL$ relationship. CL_{Sex} , $CL_{D<4}$, $CL_{D \geq 4}$ and CL_{TDD} are the coefficients for the effects of sex, surgery and dose on $CL_{NR,F}$.

Data S4: Equations for CL/F simulations for edoxaban

Krekels EH et al (2016) PMID 26951208 ¹²

$$CL/F = CL_{nr}/F + CL_r/F$$

$$CL_{nr\ NVAF\ patients}/F = \theta_{20} \cdot \text{Typical value } CL_{nr\ volunteer}/F = 0.845 \cdot 13.8 \text{ L/h} = 11.66 \text{ L/h}$$

$$\text{Fraction } (\theta_{20}) \text{ of apparent non - renal clearance } (CL_{nr}/F) \text{ for NVAF patients} = 0.845$$

$$CL_r/F = \text{slope}_1 \cdot CL_{Cr}$$

$$\text{Slope}_1 = 0.196$$

The fractional change in CL/F with concomitant P - gp inhibitor: Typical $CL/F_{\text{without Pgp-inhibitor}} \cdot (1 + \theta_{17})$

Fractional change $(1 + \theta_{17})$ in total apparent clearance (CL/F) with coadministration of P - gp inhibitors for healthy volunteers = 0.315

$$\text{Typical } F_{\text{with Pg-p inhibitor NVAF patients}} = \text{Typical } F_{\text{without Pg-p inhibitor NVAF patients}} \cdot (1 + \theta_{18} \cdot \theta_{25})$$

$$(1 + \theta_{18}) = \text{fractional change in relative } F \text{ with coadministration of Pgp inhibitors for healthy volunteers} = 1.20$$

$$\theta_{25} = \text{fraction of change in relative } F \text{ with concomitant P - gp inhibitor for NVAF patient} = 0.134$$

CL_{Cr} , creatinine clearance ; CL/F , apparent total clearance; CL_{Nr} , apparent non renal clearance; CL_{Fr} , apparent renal clearance; NVAF, non-valvular atrial fibrillation

Niebecker R et al (2015) PMID 26218447 ¹³

$$CL/F = CL_{nr}/F + CL_r/F$$

$$CL_r/F = \theta_1 \cdot CL_{Cr}$$

$$\theta_1 = 0.199 \text{ (slope 1)}$$

$$CL_{nr}/F = CL_{nr,pop} \cdot \left(\frac{WT}{70} \right)^{3/4}$$

Only for phase 3: Typical $F_{\text{with } Pg-p \text{ inhibitor}} = \text{Typical } F_{\text{without } Pg-p \text{ inhibitor}} \cdot (1 + \theta_{P-gp})$

$P - gp$ inhibitors on F , phase 3(%): - 11.5

CLCr, creatinine clearance ; CL/F, apparent total clearance; CL/Fnr, apparent non renal clearance; CL/Fr, apparent renal clearance; WT, weight

$$CL_{nr}/F = CL_{nr,typ} \cdot \left(\frac{WT}{70} \right)^{3/4}$$

Yin O et al (2014) PMID 25168620¹⁴

$$CL = 11.4 \cdot \left(\frac{BW}{81} \right)^{0.528} \cdot \left(\frac{Age}{63} \right)^{-0.188} + 0.0822 \cdot CLCr$$

$F_1 = 0.583$

Amiodarone on $F_1 = 0.300$

Verapamil on $F_1 = 0.382$

Ketoconazole on $F_1 = 0.57$

BW, body weight, CLCr, creatinine clearance, F_1 , Bioavailability

Salazar DE et al (2012) PMID 22398655¹⁵

$$\frac{CL}{F} = \frac{CL}{F_{pop}} \cdot \left(\frac{CLCr}{91} \right)^{0.341} \cdot e^{-(Keto_i 0.18)} \cdot e^{-(Ery_i 0.199)} \cdot e^{-(Qnd_i 0.212)} \cdot e^{-(Amio_i 0.436)}$$

$$F_i = 1 \cdot e^{(Keto_i 0.792)} \cdot e^{(Ery_i 0.781)} \cdot e^{(Qnd_i 0.727)} \cdot e^{(Amio_i 0.751)}$$

$CL/F_{pop} = 36 L/h$

CLCr, creatinine clearance, F_1 , Bioavailability

Rohatagi S et al (2012) PMID 23014669¹⁶

$$CL/F = CL/F_{pop} \cdot \left(\frac{CLCr}{81} \right)^{K_{CL/F-CLCR}}$$

$K_{CL/F-CLCR} = 0.350$

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